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NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	JUL 28	CA/CAplus patent coverage enhanced
NEWS	3	JUL 28	EPFULL enhanced with additional legal status information from the epoline Register
NEWS	4	JUL 28	IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS	5	JUL 28	STN Viewer performance improved
NEWS	6	AUG 01	INPADOCDB and INPAFAMDB coverage enhanced
NEWS	7	AUG 13	CA/CAplus enhanced with printed Chemical Abstracts page images from 1967-1998
NEWS	8	AUG 15	CAOLD to be discontinued on December 31, 2008
NEWS	9	AUG 15	CAplus currency for Korean patents enhanced
NEWS	10	AUG 27	CAS definition of basic patents expanded to ensure comprehensive access to substance and sequence information
NEWS	11	SEP 18	Support for STN Express, Versions 6.01 and earlier, to be discontinued
NEWS	12	SEP 25	CA/CAplus current-awareness alert options enhanced to accommodate supplemental CAS indexing of exemplified prophetic substances
NEWS	13	SEP 26	WPIDS, WPINDEX, and WPIX coverage of Chinese and and Korean patents enhanced
NEWS	14	SEP 29	IFICLS enhanced with new super search field
NEWS	15	SEP 29	EMBASE and EMBAL enhanced with new search and display fields
NEWS	16	SEP 30	CAS patent coverage enhanced to include exemplified prophetic substances identified in new Japanese-language patents
NEWS	17	OCT 07	EPFULL enhanced with full implementation of EPC2000
NEWS	18	OCT 07	Multiple databases enhanced for more flexible patent number searching
NEWS	19	OCT 22	Current-awareness alert (SDI) setup and editing enhanced
NEWS	20	OCT 22	WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT Applications
NEWS	21	OCT 24	CHEMLIST enhanced with intermediate list of pre-registered REACH substances

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that
specific topic.

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FILE 'HOME' ENTERED AT 14:15:22 ON 19 NOV 2008

=> file medline
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	0.42

FILE 'MEDLINE' ENTERED AT 14:16:43 ON 19 NOV 2008

FILE LAST UPDATED: 18 Nov 2008 (20081118/UP). FILE COVERS 1949 TO DATE.

MEDLINE has been updated with the National Library of Medicine's
revised 2008 MeSH terms. See HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

See HELP RANGE before carrying out any RANGE search.

MEDLINE Accession Numbers (ANs) for records from 1950-1977 have
been converted from 8 to 10 digits. Searches using an 8 or 10 digit
AN will retrieve the same record. The 10-digit ANs can be expanded,
searched, and displayed in all records from 1949 to the present.

```
=> s influenza
L1       51023 INFLUENZA

=> s l1 and sirna
          8598 SIRNA
L2          31 L1 AND SIRNA

=> s l1 and antisense
         27840 ANTISENSE
L3          86 L1 AND ANTISENSE

=> s l2 and np
         11679 NP
L4           4 L2 AND NP

=> s l3 and np
         11679 NP
L5          17 L3 AND NP

=> d l4 1-4 ab

L4   ANSWER 1 OF 4     MEDLINE on STN
AB   Avian influenza virus H5N1 causes widespread infection in the
     birds and human respiratory tract, but existing vaccines and drug therapy
     are of limited value.  Here we show that small interfering RNAs (siRNAs)
     specific for conserved regions of the viral genome can potently inhibit
     influenza virus production in cell lines, embryonated chicken eggs
     and BALB/c mice. siRNA expression plasmid pBabe-Super was chosen
     in the study, which directed the synthesis of small interfering RNAs in
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cells. The inhibition depended on the presence of a functional antisense strand in the small interfering RNA duplex, suggesting that viral mRNA is the target of RNA interference (RNAi). Among the three small interfering RNA expression plasmids we designed, we found that small interfering RNA for nucleocapsid protein (NP) had a specific effect in inhibiting the accumulation of RNAs in infected cells because of a critical requirement for newly synthesized nucleocapsid proteins in avian influenza viral RNA transcription and replication. The findings reveal that newly synthesized nucleocapsid, polymerase A (PA) and polymerase B1 (PB1) proteins are required for avian influenza virus transcription and replication and provide a basis for the development of small interfering RNAs as prophylaxis and therapy for avian influenza infection in birds and humans.

L4 ANSWER 2 OF 4 MEDLINE on STN

AB RNA interference (RNAi) is a powerful tool to silence gene expression. Small interfering RNA (siRNA)-induced RNA degradation has been recently used as an antivirus agent to inhibit specific virus replication. Here, we showed that several siRNAs specific for conserved regions of influenza virus matrix (M2) and nucleocapsid protein (NP) genes could effectively inhibit expression of the corresponding viral protein. We also evaluated the antiviral potential of these siRNAs targeting M2 and NP of H5N1 avian influenza virus (AIV), which are essential to viral replication. We investigated the inhibitory effect of M2-specific siRNAs and NP-specific siRNAs on influenza A virus (H5N1, H1N1 and H9N2) replication in Madin-Darby canine kidney (MDCK) cells and BALB/c mice. The results showed that treatment with these siRNAs could specifically inhibit influenza A virus replication in MDCK cells (0.51-1.63 TCID(50) reduction in virus titers), and delivery of pS-M48 and pS-NP1383 significantly reduced lung virus titers in the infected mice (16-50-fold reduction in lung virus titers) and partially protected the mice from lethal influenza virus challenge (a survival rate of 4/8 for H1N1 virus-infected mice and 2/8 for H5N1 virus infected mice). Moreover, the treatment of pS-M48 and pS-NP1383 could suppress replication of different subtypes of influenza A viruses, including a H5N1 highly pathogenic avian isolate strain. The results provided a basis for further development of siRNA for prophylaxis and therapy of influenza virus infection in humans and animals.

L4 ANSWER 3 OF 4 MEDLINE on STN

AB Three plasmid constructs were prepared that express small interfering RNAs (siRNAs) targeted to sequences encoding the ribonucleoprotein member, nucleoprotein (NP) and/or PA, of influenza virus genome. The antiviral properties of siRNAs against the H5N1 strain of influenza virus were studied by evaluating their capacity to silence expression of target genes as well as their effect on influenza virus-induced apoptosis in Madin-Darby canine kidney cells, chicken embryo fibroblast cells, and embryonated chicken eggs in a transient replication model. The results demonstrated that all three siRNAs expressing plasmids efficiently transcribed the short hairpin RNAs and inhibited expression of the NP or PA proteins measured by northern blot and western blot analyses, respectively, in the transfected cells. We also found that the integrated siRNA expression plasmid pEGFP/NP+PA, which we constructed for the first time to synchronously target NP and PA segments of the influenza virus genome, could more efficiently inhibit synthesis of influenza virus detected by cytopathogenic effects, hemagglutinin, and plaque-forming unit assays in the transfected cells. Furthermore, the integrated siRNA expression plasmid pEGFP/NP+PA could remarkably interrupt the cellular apoptotic course caused by influenza virus, which protected infected cells from apoptotic

damage. In contrast, a control siRNA expression plasmid, pEGFP/HK, could neither inhibit the protein expression and production of influenza virus nor interrupt the cell apoptotic course mediated by influenza virus. These results demonstrate that RNA interference (RNAi) can be used to inhibit protein expression and replication of influenza virus and that RNAi treatment holds potential as a new approach to prevent avian influenza.

L4 ANSWER 4 OF 4 MEDLINE on STN
AB Influenza A virus causes widespread infection in the human respiratory tract, but existing vaccines and drug therapy are of limited value. Here we show that short interfering RNAs (siRNAs) specific for conserved regions of the viral genome can potently inhibit influenza virus production in both cell lines and embryonated chicken eggs. The inhibition depends on the presence of a functional antisense strand in the siRNA duplex, suggesting that viral mRNA is the target of RNA interference. However, siRNA specific for nucleocapsid (NP) or a component of the RNA transcriptase (PA) abolished the accumulation of not only the corresponding mRNA but also virion RNA and its complementary RNA. These siRNAs also broadly inhibited the accumulation of other viral, but not cellular, RNAs. The findings reveal that newly synthesized NP and PA proteins are required for influenza virus transcription and replication and provide a basis for the development of siRNAs as prophylaxis and therapy for influenza infection in humans.

=> d 1-4 l4

L4 ANSWER 1 OF 4 MEDLINE on STN
AN 2008338466 MEDLINE
DN PubMed ID: 18456361
TI RNA interference of avian influenza virus H5N1 by inhibiting viral mRNA with siRNA expression plasmids.
AU Zhou Kai; He Hongxuan; Wu Yanyun; Duan Mingxing
CS National Research Center For Wildlife Born Diseases, Key Laboratory of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, PR China.
SO Journal of biotechnology, (2008 Jun 1) Vol. 135, No. 2, pp. 140-4. Electronic Publication: 2008-03-26.
Journal code: 8411927. ISSN: 0168-1656.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200809
ED Entered STN: 28 May 2008
Last Updated on STN: 23 Sep 2008
Entered Medline: 22 Sep 2008

L4 ANSWER 2 OF 4 MEDLINE on STN
AN 2007567470 MEDLINE
DN PubMed ID: 17719657
TI Effective small interfering RNAs targeting matrix and nucleocapsid protein gene inhibit influenza A virus replication in cells and mice.
AU Zhou Hongbo; Jin Meilin; Yu Zhengjun; Xu Xiaojuan; Peng Yaping; Wu Haiya; Liu Jinlin; Liu Hu; Cao Shengbo; Chen Huanchun
CS National Key Laboratory of Agricultural Microbiology, Huazhong Agricultural University, Wuhan 430070, PR China.
SO Antiviral research, (2007 Nov) Vol. 76, No. 2, pp. 186-93. Electronic Publication: 2007-08-10.

Journal code: 8109699. ISSN: 0166-3542.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200711
ED Entered STN: 25 Sep 2007
Last Updated on STN: 8 Dec 2007
Entered Medline: 27 Nov 2007

L4 ANSWER 3 OF 4 MEDLINE on STN
AN 2006019395 MEDLINE
DN PubMed ID: 16405000
TI Construction of influenza virus siRNA expression vectors and their inhibitory effects on multiplication of influenza virus.
AU Li Yao-Chen; Kong Ling-hong; Cheng Bi-Zhen; Li Kang-Sheng
CS Department of Microbiology and Immunology, Shantou University Medical College, Shantou Guangdong 515031, China.
SO Avian diseases, (2005 Dec) Vol. 49, No. 4, pp. 562-73.
Journal code: 0370617. ISSN: 0005-2086.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200602
ED Entered STN: 13 Jan 2006
Last Updated on STN: 28 Feb 2006
Entered Medline: 27 Feb 2006

L4 ANSWER 4 OF 4 MEDLINE on STN
AN 2003106165 MEDLINE
DN PubMed ID: 12594334
TI RNA interference of influenza virus production by directly targeting mRNA for degradation and indirectly inhibiting all viral RNA transcription.
AU Ge Qing; McManus Michael T; Nguyen Tam; Shen Ching-Hung; Sharp Phillip A; Eisen Herman N; Chen Jianzhu
CS Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA.
NC AI32486 (United States NIAID)
AI40146 (United States NIAID)
AI44477 (United States NIAID)
AI44478 (United States NIAID)
AI50631 (United States NIAID)
CA42063 (United States NCI)
CA60686 (United States NCI)
GM34277 (United States NIGMS)
SO Proceedings of the National Academy of Sciences of the United States of America, (2003 Mar 4) Vol. 100, No. 5, pp. 2718-23. Electronic Publication: 2003-02-19.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Priority Journals
EM 200305

ED Entered STN: 6 Mar 2003
Last Updated on STN: 14 May 2003
Entered Medline: 13 May 2003

=> d ti 1-17 l5

L5 ANSWER 1 OF 17 MEDLINE on STN
TI RNA interference of avian influenza virus H5N1 by inhibiting viral mRNA with siRNA expression plasmids.

L5 ANSWER 2 OF 17 MEDLINE on STN
TI Inhibition of influenza A H3N8 virus infections in mice by morpholino oligomers.

L5 ANSWER 3 OF 17 MEDLINE on STN
TI Morpholino oligomers targeting the PB1 and NP genes enhance the survival of mice infected with highly pathogenic influenza A H7N7 virus.

L5 ANSWER 4 OF 17 MEDLINE on STN
TI RNA interference of influenza virus production by directly targeting mRNA for degradation and indirectly inhibiting all viral RNA transcription.

L5 ANSWER 5 OF 17 MEDLINE on STN
TI Antisense therapy of influenza.

L5 ANSWER 6 OF 17 MEDLINE on STN
TI In vitro and in vivo anti-influenza A virus activity of antisense oligonucleotides.

L5 ANSWER 7 OF 17 MEDLINE on STN
TI Specific inhibition of influenza virus RNA polymerase and nucleoprotein gene expression by liposomally encapsulated antisense phosphorothioate oligonucleotides in MDCK cells.

L5 ANSWER 8 OF 17 MEDLINE on STN
TI Inhibition of influenza virus RNA polymerase by 5'-capped short RNA fragments.

L5 ANSWER 9 OF 17 MEDLINE on STN
TI Specific inhibition of influenza virus RNA polymerase and nucleoprotein gene expression by circular dumbbell RNA/DNA chimeric oligonucleotides containing antisense phosphodiester oligonucleotides.

L5 ANSWER 10 OF 17 MEDLINE on STN
TI Antisense nucleic acid therapy of influenza virus.

L5 ANSWER 11 OF 17 MEDLINE on STN
TI Specific inhibition of influenza virus RNA polymerase and nucleoprotein genes expression by liposomally endocapsulated antisense phosphorothioate oligonucleotides: penetration and localization of oligonucleotides in clone 76 cells.

L5 ANSWER 12 OF 17 MEDLINE on STN
TI Inhibition of influenza virus RNA polymerase and nucleoprotein of gene expression by antisense oligonucleotides.

L5 ANSWER 13 OF 17 MEDLINE on STN
TI Inhibition of influenza virus RNA polymerase and nucleoprotein

genes expression by unmodified, phosphorothioated, and liposomally encapsulated oligonucleotides.

L5 ANSWER 14 OF 17 MEDLINE on STN
TI The RNA polymerase PB2 subunit is not required for replication of the influenza virus genome but is involved in capped mRNA synthesis.

L5 ANSWER 15 OF 17 MEDLINE on STN
TI [Suppression of influenza virus NP-protein mRNA translation in vitro with derivatives of an antisense oligonucleotide]. Podavlenie transliatsii mRNK NP-belka virusa grippa in vitro proizvodnymi antismyslovogo oligonukleotida.

L5 ANSWER 16 OF 17 MEDLINE on STN
TI Hydrophobized antiviral antibodies and antisense oligonucleotides.

L5 ANSWER 17 OF 17 MEDLINE on STN
TI Characterisation of an avian influenza virus nucleoprotein expressed in E. coli and in insect cells.

=> d 2 3 4 5 6 7 10 11 15

L5 ANSWER 2 OF 17 MEDLINE on STN
AN 2008258755 MEDLINE
DN PubMed ID: 18369525
TI Inhibition of influenza A H3N8 virus infections in mice by morpholino oligomers.
AU Lupfer Christopher; Stein David A; Mourich Dan V; Tepper Samuel E; Iversen Patrick L; Pastey Manoj
CS Genetics Program, College of Agricultural Science, Oregon State University, Corvallis, OR 97331, USA.
SO Archives of virology, (2008) Vol. 153, No. 5, pp. 929-37. Electronic Publication: 2008-03-28.
Journal code: 7506870. ISSN: 0304-8608.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-EU236678; GENBANK-EU236679
EM 200807
ED Entered STN: 19 Apr 2008
Last Updated on STN: 4 Jul 2008
Entered Medline: 3 Jul 2008

L5 ANSWER 3 OF 17 MEDLINE on STN
AN 2008184939 MEDLINE
DN PubMed ID: 18343835
TI Morpholino oligomers targeting the PB1 and NP genes enhance the survival of mice infected with highly pathogenic influenza A H7N7 virus.
AU Gabriel Gulsah; Nordmann Alexandra; Stein David A; Iversen Patrick L; Klenk Hans-Dieter
CS Institute of Virology, Philipps University Marburg, Germany.. guelsah.gabriel@path.ox.ac.uk
SO The Journal of general virology, (2008 Apr) Vol. 89, No. Pt 4, pp. 939-48.
Journal code: 0077340. ISSN: 0022-1317.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LA English
FS Priority Journals
EM 200806
ED Entered STN: 18 Mar 2008
Last Updated on STN: 25 Jun 2008
Entered Medline: 24 Jun 2008

L5 ANSWER 4 OF 17 MEDLINE on STN
AN 2003106165 MEDLINE
DN PubMed ID: 12594334
TI RNA interference of influenza virus production by directly targeting mRNA for degradation and indirectly inhibiting all viral RNA transcription.
AU Ge Qing; McManus Michael T; Nguyen Tam; Shen Ching-Hung; Sharp Phillip A; Eisen Herman N; Chen Jianzhu
CS Center for Cancer Research and Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA.
NC AI32486 (United States NIAID)
AI40146 (United States NIAID)
AI44477 (United States NIAID)
AI44478 (United States NIAID)
AI50631 (United States NIAID)
CA42063 (United States NCI)
CA60686 (United States NCI)
GM34277 (United States NIGMS)
SO Proceedings of the National Academy of Sciences of the United States of America, (2003 Mar 4) Vol. 100, No. 5, pp. 2718-23. Electronic Publication: 2003-02-19.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 6 Mar 2003
Last Updated on STN: 14 May 2003
Entered Medline: 13 May 2003

L5 ANSWER 5 OF 17 MEDLINE on STN
AN 2001447952 MEDLINE
DN PubMed ID: 11292569
TI Antisense therapy of influenza.
AU Abe T; Mizuta T; Hatta T; Miyano-Kurosaki N; Fujiwara M; Takai K; Shigeta S; Yokota T; Takaku H
CS Department of Industrial Chemistry, Chiba Institute of Technology, 2-17-1 Tsudanuma, Narashino, 275-0016, Chiba, Japan.
SO European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, (2001 Apr) Vol. 13, No. 1, pp. 61-9.
Journal code: 9317982. ISSN: 0928-0987.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 13 Aug 2001
Last Updated on STN: 13 Aug 2001
Entered Medline: 9 Aug 2001

L5 ANSWER 6 OF 17 MEDLINE on STN
AN 1999403454 MEDLINE
DN PubMed ID: 10474246
TI In vitro and in vivo anti-influenza A virus activity of antisense oligonucleotides.
AU Abe T; Mizuta T; Suzuki S; Hatta T; Takai K; Yokota T; Takaku H
CS Department of Industrial Chemistry, Chiba Institute of Technology, Japan.
SO Nucleosides & nucleotides, (1999 Jun-Jul) Vol. 18, No. 6-7, pp. 1685-8.
Journal code: 8215930. ISSN: 0732-8311.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 12 Oct 1999
Last Updated on STN: 12 Oct 1999
Entered Medline: 30 Sep 1999

L5 ANSWER 7 OF 17 MEDLINE on STN
AN 1999092563 MEDLINE
DN PubMed ID: 9875404
TI Specific inhibition of influenza virus RNA polymerase and nucleoprotein gene expression by liposomally encapsulated antisense phosphorothioate oligonucleotides in MDCK cells.
AU Abe T; Suzuki S; Hatta T; Takai K; Yokota T; Takaku H
CS Department of Industrial Chemistry, Chiba Institute of Technology, Japan.
SO Antiviral chemistry & chemotherapy, (1998 May) Vol. 9, No. 3, pp. 253-62.
Journal code: 9009212. ISSN: 0956-3202.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 199902
ED Entered STN: 16 Feb 1999
Last Updated on STN: 16 Feb 1999
Entered Medline: 2 Feb 1999

L5 ANSWER 10 OF 17 MEDLINE on STN
AN 1998024759 MEDLINE
DN PubMed ID: 9360404
TI Antisense nucleic acid therapy of influenza virus.
AU Hatta T; Abe T; Takai K; Takaku H
CS Department of Industrial Chemistry, Chiba Institute of Technology.
SO Nippon rinsho. Japanese journal of clinical medicine, (1997 Oct) Vol. 55, No. 10, pp. 2765-71. Ref: 20
Journal code: 0420546. ISSN: 0047-1852.
CY Japan
DT (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA Japanese
FS Priority Journals
EM 199801
ED Entered STN: 22 Jan 1998
Last Updated on STN: 22 Jan 1998
Entered Medline: 7 Jan 1998

L5 ANSWER 11 OF 17 MEDLINE on STN
AN 1997242229 MEDLINE
DN PubMed ID: 9125219

TI Specific inhibition of influenza virus RNA polymerase and nucleoprotein genes expression by liposomally endocapsulated antisense phosphorothioate oligonucleotides: penetration and localization of oligonucleotides in clone 76 cells.
AU Hatta T; Takai K; Nakada S; Yokota T; Takaku H
CS Department of Industrial Chemistry, Chiba Institute of Technology, Japan.
SO Biochemical and biophysical research communications, (1997 Mar 17) Vol. 232, No. 2, pp. 545-9.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 199704
ED Entered STN: 6 May 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 22 Apr 1997

=> d 2 3 4 5 6 7 10 11 15 ab

L5 ANSWER 2 OF 17 MEDLINE on STN
AB New methods to combat influenza A virus (FLUAV) in humans and animals are needed. The H3N8 subtype virus was the cause of the pandemic of 1890 and has recently undergone cross-species transmission from horses to dogs in the USA. In 2007 H3N8 spread to Australia, a continent previously devoid of equine influenza. Here, we show that antisense-peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs), delivered by intranasal administration, are able to inhibit the replication of FLUAV A/Eq/Miami/1/63 (H3N8) in mice by over 95% compared to controls. Monitoring of body weight and immune cell infiltrates in the lungs of noninfected mice indicated that PPMO treatment was not toxic at a concentration shown to be effectively antiviral in vivo. In addition, we detected a naturally occurring mutation within the PPMO target site of a viral gene that may be the cause of resistance to one of the two antisense PPMO sequences tested. These data indicate that PPMOs targeting highly conserved regions of FLUAV are promising novel therapeutic candidates.

L5 ANSWER 3 OF 17 MEDLINE on STN
AB Peptide-conjugated phosphorodiamidate morpholino oligomers (PPMO) are single-stranded nucleic acid-analogue antisense agents that enter cells readily and can reduce gene expression by steric blocking of complementary RNA (cRNA) sequences. Here, we tested a panel of PPMO designed to target conserved sequences in the RNA genome segments encoding polymerase subunits of a highly pathogenic mouse-adapted influenza A virus (SC35M; H7N7). Three PPMO, targeting the translation start site region of PB1 or NP mRNA or the 3'-terminal region of NP viral RNA (vRNA), potently inhibited virus replication in MDCK cells. Primer extension assays showed that treatment with any of the effective PPMO led to markedly reduced levels of mRNA, cRNA and vRNA. Initially, the potential toxicity of a range of intranasally administered PPMO doses was evaluated, by measuring their effect on body weight of uninfected mice. Subsequently, a non-toxic dosing regimen was used to investigate the effect of various PPMO on SC35M infection in a mouse model. Mice administered intranasal treatment of PPMO targeting the PB1-AUG region or NP vRNA, at 3 mug per dose, given once 3 h before and once 2 days after intranasal infection with 10xLD(50) of SC35M, showed a 2 log(10) reduction of viral titre in the lungs and 50 % survival for the 16 day duration of the experiment, whereas the NP-AUG-targeted PPMO treatment resulted in 30 % survival of an otherwise lethal infection.

These data suggest that PPMO provide a useful reagent to investigate influenza virus molecular biology and may constitute a therapeutic strategy against highly pathogenic influenza viruses.

L5 ANSWER 4 OF 17 MEDLINE on STN
AB Influenza A virus causes widespread infection in the human respiratory tract, but existing vaccines and drug therapy are of limited value. Here we show that short interfering RNAs (siRNAs) specific for conserved regions of the viral genome can potently inhibit influenza virus production in both cell lines and embryonated chicken eggs. The inhibition depends on the presence of a functional antisense strand in the siRNA duplex, suggesting that viral mRNA is the target of RNA interference. However, siRNA specific for nucleocapsid (NP) or a component of the RNA transcriptase (PA) abolished the accumulation of not only the corresponding mRNA but also virion RNA and its complementary RNA. These siRNAs also broadly inhibited the accumulation of other viral, but not cellular, RNAs. The findings reveal that newly synthesized NP and PA proteins are required for influenza virus transcription and replication and provide a basis for the development of siRNAs as prophylaxis and therapy for influenza infection in humans.

L5 ANSWER 5 OF 17 MEDLINE on STN
AB The liposomally encapsulated and the free antisense phosphorothioate oligonucleotides (S-ODNs) with four target sites (PB1, PB2, PA, and NP) were tested for their abilities to inhibit virus-induced cytopathogenic effects by a MTT assay using MDCK cells. The liposomally encapsulated S-ODN complementary to the sites of the PB2-AUG initiation codon showed highly inhibitory effects. On the other hand, the inhibitory effect of the liposomally encapsulated S-ODN targeted to PB1 was considerably decreased in comparison with those directed to the PB2 target sites. The liposomally encapsulated antisense phosphorothioate oligonucleotides exhibited higher inhibitory activities than the free oligonucleotides, and showed sequence-specific inhibition, whereas the free antisense phosphorothioate oligonucleotides were observed to inhibit viral absorption to MDCK cells. Therefore, the antiviral effects of S-ODN-PB2-AUG and PA-AUG were examined in a mouse model of influenza virus A infection. Balb/c mice exposed to the influenza virus A (A/PR/8/34) strain at dose of 100 LD(50)s were treated i.v. with various doses (5-40 mg/kg) of liposomally (Tfx-10) encapsulated PB2-AUG or PA-AUG before virus infection and 1 and 3 days postinfection. PB2-AUG oligomer treated i.v. significantly prolonged the mean survival time in days (MDS) and increased the survival rates with a dose-dependent manner. We demonstrate the first successful in vivo antiviral activity of antisense administered i.v. in experimental respiratory tract infections induced with influenza virus A.

L5 ANSWER 6 OF 17 MEDLINE on STN
AB We have demonstrated that antisense phosphorothioate oligonucleotides (S-ODNs) inhibit influenza virus A replication in MDCK cells. The liposomally encapsulated and the free antisense phosphorothioate oligonucleotides with four target sites (PB1, PB2, PA, and NP) were tested for their abilities to inhibit virus-induced cytopathogenic effects by a MTT assay using MDCK cells. The liposomally encapsulated S-ODN complementary to the sites of the PB2-AUG initiation codon showed highly inhibitory effects. Therefore, the antiviral effects of S-ODN-PB2-AUG and PA-AUG were examined in a mouse model of influenza virus A infection. PB2-AUG oligomer treated i.v. significantly prolonged the mean survival time in day (MDS) and increased the survival rates with does dependent manner.

L5 ANSWER 7 OF 17 MEDLINE on STN
AB We have demonstrated that antisense phosphorothioate oligonucleotides (S-ODNs) inhibit influenza A virus replication in MDCK cells. Liposomally encapsulated and free antisense S-ODNs with four target sites (PB1, PB2, PA and NP genes) were tested for their abilities to inhibit virus-induced cytopathogenic effects in a MTT assay using MDCK cells. The liposomally encapsulated S-ODN complementary to the site around the PB2 AUG initiation codon showed highly inhibitory effects. In contrast, the inhibitory effect of the liposomally encapsulated S-ODN targeted to PB1 was considerably decreased in comparison with that directed to the PB2 target site. The liposomally encapsulated antisense S-ODNs exhibited higher inhibitory activities than the free oligonucleotides, and showed sequence-specific inhibition, whereas free antisense S-ODNs were observed to inhibit viral adsorption to MDCK cells. Liposomal preparations of oligonucleotides facilitated their release from endocytic vesicles, and thus cytoplasmic and nuclear localization was observed. The activities of the antisense S-ODNs were effectively enhanced by using the liposomal carrier. Interestingly, the liposomally encapsulated FITC-S-ODN-PB2-as accumulated in the nuclear region of MDCK cells. However, weak fluorescence was observed within the endosomes and the cytoplasm of MDCK cells treated with the free antisense S-ODNs. The cationic lipid particles may thus be a potentially useful delivery vehicle for oligonucleotide-based therapeutics and transgenes, appropriate for use in vitro or in vivo.

L5 ANSWER 10 OF 17 MEDLINE on STN
AB We have demonstrated that Antisense phosphodiester (ODNs) and phosphorothioate oligonucleotides (S-ODNs) inhibit CAT (chloramphenicol acetyltransferase) protein expression in the clone 76 cell line, which is a derivative of the murine C127 cell line. This cell line expresses the influenza virus RNA polymerase and nucleoprotein (NP) genes in response to treatment with dexamethasone. Phosphodiester, phosphorothioate, and liposomally encapsulated oligonucleotides with four target sites (PB1, PB2, PA, and NP) were synthesized and tested for inhibitory effects by a CAT-ELISA assay using the clone 76 cell line. The liposomally encapsulated ODNs and S-ODNs complementary to the sites of the PB2-AUG and PA-AUG initiation codons showed highly inhibitory effects. On the other hand, the inhibitory effect of the S-ODNs targeted to PB1 was considerably decreased in comparison with the other three target sites. Liposome encapsulation afforded oligomer protection in serum-containing medium and substantially improved cellular accumulation. The liposomally encapsulated oligonucleotides exhibited higher inhibitory activity than the free oligonucleotides. Liposomal preparations of oligonucleotides facilitate release from endocytic vesicles, and thus, cytoplasmic and nuclear localization are observed following cell treatment. The activities of the unmodified oligonucleotides are effectively enhanced by using the liposomal carrier. In the observation of the endocapsulated antisense phosphodiester oligonucleotide, FITC-ODN-PB2-as treated clone 76 cells by a confocal laser scanning microscope, diffuse fluorescence was apparently observed in the cytoplasm. Interestingly, the endocapsulated antisense phosphorothioate oligonucleotide, FITC-S-ODN-PB2-as accumulated in the nuclear region of clone 76 cells. However, weak fluorescence was observed on the endosomes and in the cytoplasmes of the free antisense phosphorothioate oligonucleotides treated clone 76 cells.

L5 ANSWER 11 OF 17 MEDLINE on STN
AB Liposomally encapsulated phosphorothioate oligonucleotides with four target sites (PB1, PB2, PA, and NP) were synthesized and tested for inhibitory effects by a CAT-ELISA assay using the clone 76 cell line. The liposomally encapsulated phosphorothioate oligonucleotides (S-ODNs)

AB complementary to the sites of the PB2-AUG and PA-AUG initiation codons showed highly inhibitory effects. Displacement of the target AUG initiation codon sequence to the 3'-end, 5'-end, and/or center sites on the antisense phosphorothioate oligonucleotides was studied with regard to the inhibition of influenza virus RNA polymerases and NP. The antisense phosphorothioate oligonucleotide containing the AUG initiation codon at the center site of the oligonucleotide had the highest inhibitory effects. The liposomally encapsulated phosphorothioate oligonucleotides exhibited higher inhibitory activity than the free oligonucleotides. Observation of clone 76 cells treated with the endocapsulated antisense phosphodiester oligonucleotide, FITC-ODNs-PB2-T3, by a confocal laser scanning microscope, revealed diffuse fluorescence, apparently within the cytoplasm. Interestingly, the endocapsulated antisense phosphorothioate oligonucleotide, FITC-S-ODNs-PB2-T3 accumulated in the nuclear region of clone 76 cells. However, weak fluorescence was observed in the endosomes and in the cytoplasms of the clone 76 cells treated with the free antisense phosphorothioate oligonucleotides.

```
=> s short hairpin
        355522 SHORT
          8537 HAIRPIN
L6        1347 SHORT HAIRPIN
                 (SHORT(W)HAIRPIN)

=> s l6 and induce sequence-specific silencing
        212256 INDUCE
        855815 SEQUENCE
       1187616 SPECIFIC
         18470 SILENCING
             1 INDUCE SEQUENCE-SPECIFIC SILENCING
                 (INDUCE(W)SEQUENCE(W)SPECIFIC(W)SILENCING)
L7           1 L6 AND INDUCE SEQUENCE-SPECIFIC SILENCING

=> d

L7   ANSWER 1 OF 1     MEDLINE on STN
AN   2002222768     MEDLINE
DN   PubMed ID: 11959843
TI   Short hairpin RNAs (shRNAs) induce
     sequence-specific silencing in mammalian
     cells.
AU   Paddison Patrick J; Caudy Amy A; Bernstein Emily; Hannon Gregory J;
     Conklin Douglas S
CS   Watson School of Biological Sciences, Cold Spring Harbor, New York 11724,
     USA.
NC   R01-GM62534 (United States NIGMS)
SO   Genes & development, (2002 Apr 15) Vol. 16, No. 8, pp. 948-58.
     Journal code: 8711660. ISSN: 0890-9369.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
     (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA   English
FS   Priority Journals
EM   200205
ED   Entered STN: 18 Apr 2002
     Last Updated on STN: 14 May 2002
     Entered Medline: 13 May 2002
```

```
=> s system and stable expression
      1436546 SYSTEM
       239628 STABLE
       954226 EXPRESSION
         2473 STABLE EXPRESSION
                (STABLE(W)EXPRESSION)
L8          516 SYSTEM AND STABLE EXPRESSION

=> s l8 and short interfering rnas
       355522 SHORT
        34052 INTERFERING
        25227 RNAS
          427 SHORT INTERFERING RNAS
                (SHORT(W)INTERFERING(W)RNAS)
L9            2 L8 AND SHORT INTERFERING RNAS

=> s l9 and mammalian cells
       171191 MAMMALIAN
      2093784 CELLS
        29118 MAMMALIAN CELLS
                (MAMMALIAN(W)CELLS)
L10           1 L9 AND MAMMALIAN CELLS

=> d

L10  ANSWER 1 OF 1     MEDLINE on STN
AN   2002228055     MEDLINE
DN   PubMed ID: 11910072
TI   A system for stable expression of
     short interfering RNAs in mammalian
     cells.
AU   Brummelkamp Thijn R; Bernards Rene; Agami Reuven
CS   Division of Molecular Carcinogenesis, Division of Tumor Biology, The
     Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam,
     Netherlands.
SO   Science (New York, N.Y.), (2002 Apr 19) Vol. 296, No. 5567, pp. 550-3.
     Electronic Publication: 2002-03-21.
     Journal code: 0404511. E-ISSN: 1095-9203.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   200205
ED   Entered STN: 20 Apr 2002
     Last Updated on STN: 5 Jan 2003
     Entered Medline: 13 May 2002


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                                                      ENTRY    SESSION
FULL ESTIMATED COST                                   11.95      12.37

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FULL ESTIMATED COST	0.96	13.33

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